Remarks

I. Support for Amendments

Support for the amendments to the claims can be found in the specification, *inter alia*, at page 17, lines 3-5.

II. Status of the Claims

Reconsideration of this application is respectfully requested.

By the foregoing amendments, claim 50 is sought to be amended. These changes introduce no new matter, and their entry is respectfully requested.

Upon entry of the foregoing amendments, claims 50-59 and 74-76 are pending in the application, with claim 50 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

III. Summary of the Office Action

In the Office Action dated January 26, 2005, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

IV. Summary of the Interview

Applicants wish to thank Examiner Saidha for the time taken to discuss the present application with Applicants' representatives during a personal interview held on April 21, 2005. During this interview, the claims, cited art and the Office Action were

discussed. Applicants indicated during the interview that they would consider submitting data relevant to the outstanding rejections in a Rule 132 Declaration, and the Examiner indicated that he would reconsider the outstanding rejections in view of Applicants' submissions.

V. The Rejection Under 35 U.S.C. § 102(b) Is Traversed

In section 5 of the Office Action at pages 2-6, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as anticipated by Lee *et al.*, *Science 239*: 1288-1291 (1988) (hereinafter "Lee"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that Lee discloses the purification of porcine and murine tetrameric uricases that contain at least about 90% tetrameric uricase because the reference mentions that porcine and murine urate oxidase were "purified to homogeneity." *See* Lee at page 1289. The Examiner thus interprets a "homogeneous" preparation of uricase in Lee to encompass at least 90% of the uricase in tetrameric form. *See* Office Action at pages 4-5. Furthermore, the Examiner points to a statement in Lee that mammalian uricase "is associated with the peroxisome and exists as a tetramer with an apparent subunit size of 32,000 daltons" to support his contention that the mammalian uricase disclosed in Lee was 100% in the tetrameric form. Applicants respectfully disagree with this interpretation for at least the following reasons.

First, Lee does not expressly disclose the purification of *tetrameric* mammalian uricase as recited by the claims of the present application. This reference only indicates that porcine liver and murine urate oxidase were purified to homogeneity. This reference does *not* indicate that at least about 90% of the "purified" uricase was in a tetrameric

form. Indeed, the reference does not indicate in *what* form the "purified" uricase was, let alone that at least about 90% of it was in a tetrameric form.

Second, while mammalian uricase exists *in vivo* as a tetramer, isolated preparations of natural and recombinant uricase, as indicated in the present specification, usually contain a *mixture* of forms of the enzyme, including non-tetrameric aggregates in addition to the tetrameric form. *See* specification at page 16, lines 5-16. The estimated percentage of the non-tetrameric aggregated form of the enzyme present in such "purified" preparations varies from more than 10% to about 80%. *See id.*

This conclusion is further supported by the data presented in the accompanying Declaration Under 37 C.F.R. § 1.132 by Merry R. Sherman, Ph.D. (hereinafter "the Sherman Declaration"). These data clearly show that isolated preparations of natural and recombinant uricase, such as those prepared by the methods of Lee, contain multiple forms of the uricase, including octamers and larger aggregates. As is shown in Figures 1 and 2 (top panel) of the Sherman Declaration, the octamers and larger aggregates account for greater than about 10% of the uricase present in these preparations. However, when uricase is purified according to the methods disclosed in the present application at least about 90% of the uricase is present in a tetrameric form, with less than about 10% in a non-tetrameric aggregated form. *See* Figures 1 and 2 (bottom panel) of Sherman Declaration. Hence, as described in the present specification, and clearly shown in the accompanying Sherman Declaration, without specifically purifying their uricase preparations to enrich for the tetrameric form over all other forms, the authors of Lee would not be expected to have produced a uricase preparation in which at least about 90% of the uricase is in a tetrameric form. Instead, the uricase preparations of Lee would

be expected to contain uricase in which greater than about 10% was in a non-tetrameric aggregated form, analogous to that shown in the top panels of Figures 1 and 2 of the Sherman Declaration.

Finally, the Examiner is respectfully reminded that the method employed and cited by Lee for assessing the homogeneity of the murine urate oxidase preparations disclosed in that reference confirms that Lee is analyzing *monomeric* subunits of uricase rather than the tetrameric form of the enzyme. *See* T.G. Conley and D.G. Priest, "Purification of Uricase from Mammalian Tissue," *Preparative Biochemistry* 9:197-203 (1979) (hereinafter "Conley"). Conley (and therefore Lee, *citing* Conley at page 1289, 2nd column) used SDS/PAGE to analyze the uricase, which as the Examiner acknowledged, would dissociate any uricase tetramers (and, indeed, even larger aggregates) that might be present into monomeric subunits. Hence, Conley (and therefore Lee) clearly is only identifying monomeric forms of uricase, rather than tetrameric forms of uricase. Lee does not even mention *purifying a tetrameric form of uricase*, disclosing only the purification of uricase monomers. Thus, it is clear from the Conley reference that Lee, in disclosing "purification to homogeneity" of porcine and murine uricases, is preparing uricase *monomers* and *not* uricase preparations in which at least about 90% of the uricase is tetrameric, as is presently claimed. That is, "homogeneity" in Lee does not mean greater than about 90% tetrameric -- only that the uricase has been purified away from non-uricase contaminants. This statement in Lee relating to homogeneity thus says nothing about the form, tetrameric or otherwise, in which the uricase of Lee exists.

Thus, as one of ordinary skill would readily appreciate, Lee does not disclose the production of mammalian uricases having the characteristics recited in the present claims. Nevertheless, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1, as suggested by the Examiner during the interview, to recite "[a]n isolated tetrameric mammalian uricase, wherein at least about 90% of said uricase is in a tetrameric form and less than about 10% of said uricase is in a larger non-tetrameric form."

Under 35 U.S.C. § 102, a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can be anticipated by a publication only if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The Examiner has pointed to no express disclosure in Lee that would support the Examiner's statement that the "homogeneous preparations of porcine or murine tetrameric uricase comprises the at least about 90% tetrameric form of mammalian uricase claimed." Office Action at page 3. Furthermore, the present specification and the accompanying Sherman Declaration clearly show that by preparing uricases according to the methods of Lee, one of ordinary skill at best would succeed in preparing uricases that contain *less*

than about 90% tetrameric uricase. Thus, any reliance upon inherent anticipation by Lee is factually and legally unfounded.

Accordingly, Lee does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Lee does not anticipate claims 50-53. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) over Lee therefore are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In section 6 of the Office Action at pages 6-10, the Examiner has rejected claims 74-76 under 35 U.S.C. § 103(a) over Lee in view of Caput *et al.*, U.S. Patent No. 5,382,518 (hereinafter "Caput"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In order to establish a *prima facie* case of obviousness, all of the elements of the claims must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, the Examiner can satisfy the requisite burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the

invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

Claim 74 (and thus the remaining claims depending therefrom) is drawn to a pharmaceutical composition for lowering uric acids levels in a body fluid or tissue where the composition comprises an isolated tetrameric mammalian uricase and a pharmaceutically acceptable carrier, wherein at least about 90% of the uricase is in the tetrameric form and less than about 10% of the uricase is in a non-tetrameric aggregated form. Applicants reiterate and incorporate by reference herein the remarks made above with respect to Lee, which therefore is deficient as a primary reference for use in supporting an obviousness rejection.

These deficiencies are not cured by the disclosure of Caput. Caput does not disclose, suggest, or otherwise contemplate isolated tetrameric mammalian uricases and a pharmaceutically acceptable carrier, wherein at least about 90% of the uricase is in the tetrameric form and less than about 10% of the uricase is in a non-tetrameric aggregated form. Therefore, the disclosure of Lee, alone or in combination with that of Caput, does not disclose, suggest or contemplate the presently claimed pharmaceutical compositions for lowering uric acid levels in a body fluid or tissue where the composition comprises an isolated tetrameric mammalian uricase and a pharmaceutically acceptable carrier,

wherein at least about 90% of the uricase is in the tetrameric form and less than about 10% of the uricase is in a non-tetrameric aggregated form.

Applicants have established above that the references cited by the Examiner fail to teach all of the elements of the present claims. Therefore, it follows that a combination of the disclosures of these references would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine disclosures of the cited references. To this end, Applicants provide the following additional remarks.

As an initial matter, in their Reply Under 37 C.F.R. § 1.111 filed November 2, 2004, Applicants clearly presented why one of ordinary skill in the art would not have been motivated to combine the references of Lee and Caput to arrive at the claimed invention. In response to these statements, in the present Office Action, the Examiner stated that:

> [a]pplicants arguments have been considered but not found persuasive, because they are based on cited information not present in the specification as pointed out. Applicants point to specification at page 2, lines 18-19 and 24-28, in supporting their conclusion(s). However, there is no adequate basis in the specification for such a conclusion, at least not a the page(s)/lines as pointed out by the Applicants, and the conclusion that one of ordinary skill in the art would be more likely be motivated away from using mammalian uricase to achieve the presently claimed invention.

Office Action at page 9.

Applicants are puzzled by this statement given that the specification, as cited by the Applicants, clearly discloses the exact language pointed out by the Applicants in the Office Action response filed on November 2, 2004. As another source of this information, Applicants respectfully direct the Examiner to paragraphs 0004-0005 (page 1) in the published application of Williams *et al.*, U.S. 2003/0166249, which corresponds to the cited text in the specification as filed:

> Humans do not produce enzymatically active uricase, as a result of several mutations in the gene for uricase acquired during the evolution of higher primates. . . . Since uricase is a foreign protein in humans, however, even the first injection of the unmodified protein from *Aspergillus flavus* has induced anaphylactic reactions in several percent of treated patients, and immunologic responses limit its utility for chronic or intermittent treatment.
>
> Uricases derived from animal organs are nearly insoluble in solvents that are compatible with safe administration by injection. . . . Enzymes based on the deduced amino acid sequences of uricases from mammals, including pig and baboon, or from insects, such as, for example, *Drosophila melanogaster* or *Drosophila pseudoobscura*, have not been suitable candidates for clinical use, due to problems of immunogenicity and insolubility at physiological pH.

Published application of Williams *et al.*, U.S. 2003/0166249 at paragraphs 0004-0005 (page 1). Hence, Applicants respectfully disagree with the Examiner's statements on this issue in the present Office Action, and request clarification on the record.

In supporting this rejection, the Examiner states that one of ordinary skill in the art would have been motivated to:

> substitute *Aspergillus* uricase...with the mammalian uricase ... in developing pharmaceutical compositions for lowering uric acid in body fluid of man . . . . in view of the knowledge that man belongs to the class of mammals and a uricase originating from a mammalian species will be more

> compatible and perhaps more effective in lowering uric acid in man.

Office Action at pages 6-7. Applicants respectfully disagree with these contentions. To the contrary, a person of ordinary skill in the art would *not* have been motivated to use mammalian uricase as a substitute for *Aspergillus* uricase simply because "man belongs to the class of mammals," for at least two reasons: immunogenicity and insolubility.

First, as pointed out in the specification, enzymes based on the deduced amino acid sequences of uricases from mammals, including pig and baboon, have been shown not to be suitable candidates for human clinical use due to problems of immunogenicity. Specifically, since humans do not produce uricase (*see* Specification at page 1, lines 24-26 and U.S. 2003/0166249 at page 1, paragraph 0004), uricases from *any* other species, including other mammals, would be recognized as foreign by the human immune system and would be rapidly cleared or, in some hypersensitive humans, may lead to anaphylactic reactions (*see* Specification at page 2, lines 1-7 and 24-28 and U.S. 2003/0166249 at page 1, paragraph 0004). In either case, such immunogenicity would render the unmodified mammalian uricases virtually ineffective as human therapeutic agents. For this reason alone, then, one of ordinary skill would not have been motivated to use uricases from other mammalian species instead of *Aspergillus* uricase.

Second, as also pointed out in the specification, enzymes based on the deduced amino acid sequences of uricases from mammals, including pig and baboon, have been shown not to be suitable candidates for human clinical use due to problems of insolubility. Specifically, it is known that unmodified uricases obtained from mammals "are nearly insoluble in solvents that are compatible with safe administration by injection." Specification at page 2, lines 18-19 and 24-28 and U.S. 2003/0166249 at

page 1, paragraph 0005. Thus, even apart from the immunogenicity problems noted above, one of ordinary skill would not have been motivated to use uricases from other mammalian species instead of *Aspergillus* uricase due to the insolubility of these unmodified uricases at physiological pH.

Hence, the use in humans of mammalian uricases instead of *Aspergillus* uricase would not be expected to overcome the immunogenicity problems associated with the latter, and would instead lead to a second problem: enzyme insolubility at physiological pH. Therefore, given these problems associated with the use of mammalian uricases in humans, one of ordinary skill in the art would not have been motivated to make the Examiner's proposed substitution of mammalian uricase for *Aspergillus* uricase to achieve the presently claimed invention. Indeed, just the *opposite* is true -- one of ordinary skill would more likely have been motivated *away* from using mammalian uricases in treating humans, since attempts to use unmodified mammalian uricases in humans leads to additional problems beyond those seen with the use of *Aspergillus* uricase. Thus, it is simply incorrect to assume that because humans are mammals, the use of uricases from other mammalian species might somehow be "more compatible" or "more effective" in humans *per se*.

Thus, based on the remarks above, Applicants submit that the skilled artisan would have found no motivation to combine or modify the disclosures of the cited references so as to make and use the presently claimed invention. Accordingly, a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection of claims 74-76 under 35 U.S.C. § 103(a) over Lee in view of Caput are respectfully requested.

VII. Obviousness Type Double-Patenting Rejection

In section 7 of the Office Action at pages 10-11, the Examiner has rejected claims 50-59 and 74-76 under the judicially created doctrine of obviousness type double-patenting as being unpatentable over claims 1-30 of U.S Patent No. 6,783,965 (hereinafter "the '965 patent"). Applicants respectfully traverse this rejection. However, Applicants respectfully request that this rejection be held in abeyance until subject matter that is otherwise patentable is identified, at which time Applicants will consider filing a terminal disclaimer.

VIII. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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